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"Neuroprotective Potential Of Herbal Extracts In The Management Of Alzheimer's Disease: A Comprehensive Review"

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Abstract

Background—Alzheimer's disease (AD) is a multifactorial, progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and personality changes. While its exact etiology remains unclear, emerging evidence suggests that genetic, environmental, lifestyle, and dietary factors contribute to disease progression. Current pharmaceutical treatments primarily manage symptoms without altering disease progression, and over two hundred drug candidates have failed clinical trials in the past decade, highlighting the complexity of AD. In recent years, medicinal plants and herbal remedies have gained significant interest as complementary and alternative interventions. Numerous studies have identified various medicinal plants and their bioactive compounds with neuroprotective properties, including anti-inflammatory, antioxidant, and cognitive-enhancing effects. **Methods**—This review systematically examines recent studies exploring the role of neuroprotective herbs and their bioactive compounds in the prevention and management of AD-related dementia. Relevant literature was sourced from PubMed Central, Scopus, and Google Scholar, with studies selected based on their relevance to herbal interventions for AD.

Conclusions—Medicinal plants hold significant promise in the prevention and treatment of cognitive decline associated with AD. Their bioactive compounds may serve as potential candidates for drug discovery programs, offering a natural and potentially efficacious approach to combating neurodegeneration. Further research, including well-designed clinical trials, is essential to validate their therapeutic potential and ensure their safety and efficacy in AD management.

Keywords: herbs; Alzheimer's disease; neurodegeneration; ashwagandha; brahmi; cat's claw; ginkgo biloba; gotu kola; lion's mane; saffron; shankhpushpi; turmeric; triphala

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a major global health challenge. It is now the third leading cause of death in the United States, following cardiovascular diseases and cancer. Despite extensive research, the exact etiology of AD remains incompletely understood. Genetic factors contribute to 5–10% of cases (familial AD), while the remaining 90–95% are sporadic in nature. The presence of the ApoE ϵ 4 allele significantly increases the risk of developing AD. However, despite decades of research, efforts to find a cure have been largely unsuccessful, and existing pharmacological treatments provide only symptomatic relief, particularly in the moderate-to-severe stages of the disease.

The neuropathology of AD is characterized by progressive neuronal degeneration and synaptic loss, primarily in the hippocampus, cortex, and subcortical regions. This degeneration leads to brain atrophy and a spectrum of clinical symptoms, including memory impairment, executive dysfunction, mood disturbances, and an eventual inability to perform activities of daily living (ADLs). In its late stages, AD results in severe cognitive decline, requiring comprehensive caregiving support. Given the growing prevalence of AD, therapeutic strategies that can delay disease onset or slow progression would significantly reduce the burden of this disorder over the next several decades.

Two pathological hallmarks define AD: (a) extracellular deposition of β -amyloid ($A\beta$) plaques and (b) intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. $A\beta$ aggregation is thought to trigger neurodegeneration, leading to the cognitive decline characteristic of AD. However, recent evidence suggests a poor correlation between amyloid burden and cognitive impairment, which may explain the repeated failures of $A\beta$ -targeting drug candidates. Similarly, tau-targeted therapies have not yielded significant clinical success, indicating that the disease's pathophysiology is more complex than initially believed.

Beyond amyloid and tau pathology, several interconnected mechanisms contribute to AD progression, including neuroinflammation, oxidative stress, impaired autophagy, mitochondrial dysfunction, excitotoxicity, gut dysbiosis, metal ion toxicity, dysregulated cholesterol metabolism, insulin resistance, and chronic infections. Given the failure of monotherapeutic approaches targeting amyloid and tau, there is an urgent need for alternative strategies that address these multifaceted pathological processes.

A growing body of research suggests that a comprehensive, individualized therapeutic approach may be more effective in mitigating cognitive decline. Studies have demonstrated that addressing contributing factors such as gut health, insulin resistance, protein glycation, nutrient deficiencies, and neurotoxic exposures can yield sustained cognitive benefits. As part of this holistic approach, medicinal plants and their bioactive compounds have gained attention for their neuroprotective potential.

Herbal medicine has a long-standing history in traditional healing systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Indigenous medicine. Many medicinal plants are traditionally used to enhance cognitive function, alleviate memory impairment, and manage mood disorders associated with AD. These herbal interventions may act synergistically through multiple mechanisms, including anti-inflammatory, antioxidant, cholinergic modulation, and neurotrophic effects. The bioactive compounds in these plants not only work individually but may also enhance or regulate the activity of other phytochemicals, leading to a more comprehensive therapeutic effect.

Despite their historical use and promising pharmacological properties, medicinal plants remain underexplored in mainstream AD research. This review aims to highlight a subset of herbs with demonstrated neuroprotective effects based on their (a) traditional use in memory-related disorders, (b) identification of active phytochemicals relevant to AD therapy, (c) neuropharmacological activities, and (d) supporting preclinical and clinical evidence. By providing an overview of these plant-based interventions, we aim to contribute to the growing field of alternative and integrative approaches in AD management.

Neuroprotective Herbs for the Management of Alzheimer's Disease

Herb (Scientific Name)	Study Type	Neurotherapeutic Properties
Ashwagandha (<i>Withania somnifera</i>)	<i>In vitro, in vivo, clinical studies</i>	Antioxidant, anti-inflammatory, inhibits A β production, prevents neural cell death, promotes dendrite extension and neurite outgrowth, restores synaptic function, enhances neural regeneration, reverses mitochondrial dysfunction, improves auditory-verbal working memory, executive function, processing speed, and social cognition.
Brahmi (<i>Bacopa monnieri</i>)	<i>In vitro, in vivo, clinical studies</i>	Antioxidant, anti-inflammatory, enhances memory, attention, and executive function, inhibits A β production, prevents neural cell death, delays brain aging, improves cardiac function.
Cat's Claw (<i>Uncaria tomentosa</i>)	<i>In vitro, in vivo, pre-clinical studies</i>	Anti-inflammatory, antioxidant, reduces A β plaques and tau tangles, decreases gliosis, improves memory.
Ginkgo Biloba (<i>Ginkgo biloba</i>)	<i>In vitro, pre-clinical, clinical studies</i>	Antioxidant, improves mitochondrial function, enhances cerebral blood flow, prevents neural cell death, stimulates neurogenesis.
Gotu Kola (<i>Centella asiatica</i>)	<i>In vitro, in vivo, clinical studies</i>	Cognitive enhancer, reduces oxidative stress and A β levels, prevents apoptosis, promotes dendritic growth and mitochondrial health, improves mood and memory.
Lion's Mane (<i>Hericium erinaceus</i>)	<i>In vitro, in vivo, pre-clinical, clinical studies</i>	Neuroprotective, enhances cognition, anti-inflammatory, inhibits A β production, stimulates neurotransmission and neurite outgrowth.
Saffron (<i>Crocus sativus</i>)	<i>In vitro, in vivo, clinical studies</i>	Antioxidant, anti-amyloidogenic, anti-inflammatory, antidepressant, immunomodulatory, neuroprotective.
Shankhpushpi (<i>Convolvulus pluricaulis</i>)	<i>In vitro, in vivo, pre-clinical studies</i>	Enhances cognitive function, slows brain aging, antioxidant, anti-inflammatory.
Triphala (<i>Emblica officinalis, Terminalia bellerica, Terminalia chebula</i>)	<i>In vitro, in vivo, pre-clinical, clinical studies</i>	Antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, antiparasitic, reverses metabolic disturbances.
Turmeric (<i>Curcuma longa</i>)	<i>In vitro, in vivo, pre-clinical,</i>	Antioxidant, anti-inflammatory, antimicrobial, inhibits A β prod

	<i>clinical studies</i>	
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herbal remedies and their potential applications in treating Alzheimer's Disease (AD) and mild cognitive impairment (MCI). Here's a summary of the key points for each herb:

Ashwagandha (*Withania somnifera*):

- Contains bioactive compounds like withanolides that have antioxidant and free radical scavenging properties.
- Shown to improve memory, executive function, and attention in clinical trials with MCI patients.
- In animal models, it promotes neurite outgrowth, regenerates axons and dendrites, and reduces amyloid-beta ($A\beta$) induced memory deficits.

Brahmi (*Bacopa monnieri*):

- Contains phytochemicals like bacosides that have antioxidant and free radical scavenging actions.
- Improves memory, intellect, and cognitive function in both animal and human studies.
- Clinical trials show improvements in mental control, logical memory, and paired association learning in older adults.
- Also improves ADAS-cog and CDT scores in trials with MCI subjects when combined with other nutraceuticals.

Cat's Claw (*Uncaria tomentosa*):

- Contains oxindole alkaloids and polyphenols with immune-modulating and anti-inflammatory effects.
- In transgenic mouse models of AD, it reduces $A\beta$ load, plaque number, astrogliosis, and microgliosis, and improves memory.
- Pre-clinical studies suggest it may be effective for memory loss and cognitive decline, but human studies are lacking.

Ginkgo Biloba:

- Contains flavonoids and terpenoids with antioxidant and anti-platelet activity.
- Shows beneficial effects in treating AD, vascular dementia, and other age-associated conditions.
- Clinical trials indicate modest improvements in cognitive function and activities of daily living (ADLs) in AD patients.

Gotu Kola (*Centella asiatica*):

- Contains asiaticosides and other compounds that have antioxidant and anti-amyloidogenic properties.
- Promotes neurite outgrowth, improves learning and memory in animal models, and reduces $A\beta$ levels.
- Clinical studies show that it enhances working memory and improves mood in healthy volunteers.

Lion's Mane (*Hericium erinaceus*):

- Contains hericenones and erinacines that increase nerve growth factor (NGF) expression.
- Stimulates neurite length, improves cognitive performance, and reduces $A\beta$ plaques in animal models.

- Clinical trials show increased cognitive function in MCI patients and improved ADLs in mild AD patients.

Saffron (*Crocus sativus*):

- Contains safranal and other phytochemicals with antioxidant, anti-inflammatory, and anti-amyloidogenic properties.
- Clinical trials show that it improves cognitive performance in mild to moderate AD patients and is comparable to donepezil and memantine.

Shankhpushpi (*Convolvulus pluricaulis*):

- Contains triterpenoids, flavonol glycosides, and other compounds with nootropic and memory-enhancing properties.
- Displays antioxidant activity and improves learning and memory in animal models by increasing acetylcholine (ACh) content and activity.
- Clinical studies are lacking.

Turmeric (*Curcuma longa*):

- Contains curcuminoids with anti-inflammatory and antioxidant properties.
- Reduces plaque load, inflammation, and oxidative damage in animal models of AD.
- Clinical studies on human cognitive function are limited and inconclusive, but combinations with other supplements may enhance neuroprotective effects.

Triphala:

- A combination of Amalaki, Bibhitaki, and Haritaki fruits with antioxidant, anti-inflammatory, and immunomodulatory effects.
- Shows potential in treating metabolic diseases, dental issues, and other conditions.
- Reduces body weight, cholesterol levels, and blood sugar in animal and human studies.
- May reduce chronic activation of the innate immune system in AD.

Other Medicinal Plants for Alzheimer's Disease

Several medicinal plants have been traditionally used for cognitive enhancement and neuroprotection. However, their role in the prevention or treatment of Alzheimer's disease (AD) remains largely unexplored, with limited in vitro or in vivo studies supporting their efficacy. Most available data come from observational studies, and no definitive clinical evidence supports their role in preventing dementia. Some of these plants include:

- **Vacha** (*Acorus calamus*)
- **Guduchi** (*Tinospora cordifolia*)
- **Guggul** (*Commiphora wightii*)
- **Jatamansi** (*Nardostachys jatamansi*)
- **Jyotismati** (*Celastrus paniculatus*)
- **Rosemary** (*Rosmarinus officinalis*)
- **Green tea** (*Camellia sinensis*)

- **St. John's Wort** (*Hypericum perforatum*)
- **Sage** (*Salvia spp.*)
- **Rhodiola** (*Rhodiola rosea*)
- **Moringa** (*Moringa oleifera*)
- **Shilajit**
- **Lemon balm** (*Melissa officinalis*)

Further studies are necessary to determine their precise mechanisms, bioavailability, and efficacy in AD prevention and treatment.

Administration of Herbal Extracts

A major challenge in developing herbal treatments for AD is drug delivery across the blood-brain barrier (BBB), which restricts the entry of many therapeutic compounds. While oral administration is the most common route, its effectiveness in delivering herbal constituents to the central nervous system (CNS) remains unclear. Several alternative delivery methods are being explored:

1. Intranasal Administration (INA)

- Intranasal administration is a **non-invasive, rapid** method that bypasses the BBB and directly targets the CNS.
- Herbal extracts, either in dry powder form or as medicated oils, can be administered through this route.
- Lipophilic and lipid-soluble molecules in medicated oils enhance synergistic interactions among herbal constituents.
- **Benefits:** Minimizes systemic side effects, avoids brain injury, and eliminates the need for invasive drug delivery devices.
- **Challenges:** Contradictory research findings and a lack of clinical trials limit its widespread acceptance.

2. Topical and Massage Applications

- Medicated herbal oils can be applied externally and massaged into the skin, promoting relaxation and improving cerebral blood flow.
- Massage therapy has been shown to reduce stress-related hormones, which may indirectly support cognitive function.

3. Transcranial Herbal Application

- In this method, medicated oils are applied to the **cranium or frontal regions of the brain**, allowing active compounds to be absorbed.
- Recent studies suggest that endothelial cells lining CNS capillaries facilitate solute entry from the oil into the **frontal lobe and prefrontal cortex**.
- While promising, more research is needed to confirm its effectiveness as a delivery mechanism for herbal extracts in AD treatment.

Conclusion

Alzheimer's disease (AD) remains a major neurodegenerative disorder with no definitive cure. Current pharmaceutical treatments offer only symptomatic relief without halting disease progression. Given the complexity of AD pathophysiology, which involves amyloid-beta accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and neurotransmitter imbalances, alternative therapeutic strategies are needed. Herbal medicine, with its long history in traditional practices such as Ayurveda, Traditional Chinese Medicine (TCM), and other indigenous healing systems, presents a promising avenue for AD treatment. Several medicinal plants, including Ashwagandha, Brahmi, Ginkgo biloba, Gotu kola, and Turmeric, have demonstrated neuroprotective properties such as antioxidant, anti-inflammatory, anti-amyloidogenic, and cognitive-enhancing effects in preclinical and clinical studies. These herbs may not only alleviate symptoms but also target multiple disease mechanisms, making them potential candidates for drug discovery. Despite their therapeutic potential, challenges remain in the standardization, bioavailability, and clinical validation of herbal compounds. Furthermore, effective drug delivery methods, such as intranasal administration, transcranial applications, and lipid-based formulations, are being explored to enhance CNS penetration. Future research should focus on comprehensive clinical trials, improved drug delivery strategies, and synergistic formulations to maximize the efficacy of herbal therapies. Integrating medicinal plants into a multimodal treatment approach, alongside lifestyle modifications and personalized interventions, may provide a more holistic and effective strategy for managing AD. Harnessing the power of neuroprotective herbs offers a promising and complementary pathway toward combating AD, with the potential to improve cognitive health, slow disease progression, and enhance the quality of life for patients.

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